PATENT COOPERATION TREATY

by fax and post

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	07.06.2004
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
MJL/B45292	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 02/14902	30.12.2002	02.01.2002

Applicant
GLAXOSMITHKLINE BIOLOGICALS S.A., et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
MJL/B45292		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 02/14902	30.12.2002	02.01.2002

International Patent Classification (IPC) or both national classification and IPC

C07K14/195

Applicant

GLAXOSMITHKLINE BIOLOGICALS S.A., et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.07.2003	07.06.2004

Name and mailing address of the international preliminary examining authority:

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Authorized Officer

Weikl, M

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 02/14902

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-99 as originally filed

Claims, Numbers

1-30 as originally filed

Sequence listing part of the description, pages:

1-57, filed with the letter of 13.08.2003,

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-27 (partially), 29 (completely)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-27 (partially), 29 (completely)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-6, 12-28, 30
	No:	Claims	1, 2, 7-11
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-28, 30
Industrial applicability (IA)	Yes:	Claims	1-28, 30
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

For the present application a Partial Search Report under Article 3(4)(iii) in combination with Rule 13.1 PCT and under Article 17(2)(a) PCT in conjunction with Articles 5 and 6 PCT has been issued. The claims or parts of claims relating to inventions on which no international search report has been established are thus not subject of this international preliminary examination (Rule 66.1(e) PCT).
Thus, the following examination report only relates to those groups of inventions for which an International Search Report has been established i.e. claims 1-27 (insofar as they relate to SEQ ID Nos 1 and 2), 28 and 30.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: DATABASE EMBL [Online] 10 February 2001 (2001-02-10) 'Pasteurella multocida PM70 section 122 of 204 of the complete genome' Database accession no. AE006155 XP002252628 -& DATABASE SWALL [Online] 1 June 2001 (2001-06-01) 'LosA' Database accession no. Q9CLR6 XP002252629

D2: DATABASE EMBL [Online] 25 June 1996 (1996-06-25) 'Haemophilus ducreyi ribosomal protein L31, LOS biosynthesis enzyme LBGA, LOS biosynthesis enzyme LBGB and exonuclease III genes, complete cds' Database accession no. U58147 XP002252630 -& DATABASE SWALL [Online] 1 November 1996 (1996-11-01) 'LOS biosynthesis enzyme LBGA' Database accession no. Q47960 XP002252631 -& 'Identification of tandem genes involved in lipooligosaccharide expression by Haemophilus ducreyi' INFECTION AND IMMUNITY, vol. 65, no. 2, February 1997 (1997-02), pages 651-660, XP002252627

D3: POOLMAN J T ET AL: 'Developing a nontypeable Haemophilus influenzae (NTHi) vaccine' VACCINE, BUTTERWORTH SCIENTIFIC. GUILDFORD, GB, vol. 19, 8 December 2000 (2000-12-08), pages S108-S115,

XP004227958 ISSN: 0264-410X

D4: KYD J ET AL: 'Nontypeable Haemophilus influenzae: challenges in developing a vaccine' JOURNAL OF BIOTECHNOLOGY, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 73, no. 2-3, 20 August 1999 (1999-08-20), pages 103-108, XP004180173 ISSN: 0168-1656

2. Subject-matter of the searched group of inventions

The application discloses nucleotide and amino acid sequences of a protein specific for nontypeable *H. influenzae* (i.e. it can not be found in *H. influenzae* Rd strain). It is implied that the protein is involved in lipo- oligosaccharide biosynthesis based on a 62% amino acid identity to LBGA of *H. ducreyi.*

3. Novelty (Article 33(2) PCT)

Prior art document D1 discloses a protein of Pasteurella multocida which exhibits sequence identities of 97.9% on the amino acid level and 98.2% on the nucleotide level to the protein claimed by this application. The protein is identified as lipo-oligosaccharide biosynthesis related protein LosA.

Thus, D1 anticipates the subject-matter of claims 1, 2 and 7-11.

4. Inventive Step (Article 33(3) PCT)

This Authority is of the opinion that the provision of the Orf1 sequences and their use as claimed does not involve inventive activity in the sense of Article 33(3) PCT for the following reasons:

4.1 Considering the significant sequence identities to the P. multocida LosA, the identification of the corresponding ntHi homologue would have been arrived at by mere application of general laboratory techniques. Therefore, claims 1-14 do not involve an inventive step.

4.2 Dependent claims 15-18 and 22 do not disclose additional features which are on their own sufficient to establish patentability of the claimed subject.

4.3 Claims 19-21 and 25-27 relate to uses of Orf1 which are dependent on the protein's usefulness in generating an immune response. An antigenic activity which ultimately leads to immunoprotection of the recipient animal is however *a priori* not credible in the light of the relevant prior art.

For example, document D4 discloses that 'several outer membrane antigens have been eliminated as potential vaccines on the basis of surface-epitope heterogeneity or some other criteria' (page 105, right column). It thus seems that the challenge in the development of an ntHi vaccine is **not** the identification of an ntHi **specific** protein. Due to the significant sequence heterogeneity in ntHi, the difficulty resides within the provision of a protein which is **conserved** within the population (see also D3).

Therefore, without technical evidence supporting an immunoprotective function of Orf1 in ntHi infections, its use as a vaccine (as in claims 19-21 and 25-27) can not be acknowledged in order to establish inventive activity of the claimed subject-matter.

4.4 The application claims that the disclosed Orfs (including Orf1) are specific to non typeable *H. influenzae* and are thus particularly useful in the ntHi diagnostic field i.e. can be used as specific ntHi markers.
However, it must be noted that at the relevant date of this application the mere provision of a sequence, which is specific for a particular organism does not appear to be a task which requires inventive activity. The skilled person would have arrived at such a sequence with a reasonable expectation of success. (N.B: Also nothing in the cited prior art indicated that no reasonable expectation of success existed for the identification of such a marker sequence). Consequently, in the absence of evidence that Orf1 is particularly useful for detecting ntHi, its choice as an ntHi marker merely amounts to an arbitrary selection from many possible solutions.

4.5 It was already disclosed in prior art document D2 (Stevens et al.) that a change of lbga expression in H. ducreyi resulted in modification of lipo-oligosaccharide structure. The transfer of this process to ntHi does not require inventive activity.

In summary, all of claims 1-28 and 30 lack an inventive step in the sense of Article

33(3) PCT.